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1-BROMO-2-ETHOXYCYCLOPROPYLLITHIUM AS A SYNTHETIC EQUIVALENT OF 2-LITHIOPROPENAL MOIETY

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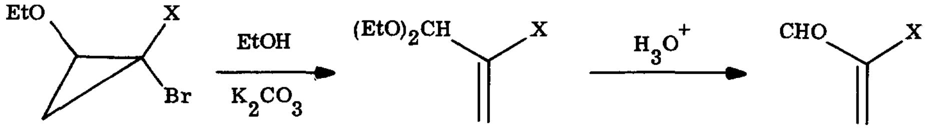
Various homologation methods of aliphatic and alicyclic systems are based on synthetic applications of stabilized carbanions. One of the most salient is the chemistry of lithium carbenoids which exist as such at low temperature and react with both electrophiles and nucleophiles.[1] The title carbenoid (Ib) now disclosed reacts with several electrophiles to produce Id-If whose subsequent ring opening gives rise to a variety of 2-substituted propenals III.

Although thermal rearrangement of 1,1-dihalo-2-alkoxycyclopropanes to 2-halopropenal derivatives is well-documented,[2,3] the stereoelectronic aspect of ring opening still remains unsolved. It has been found that the transformation of trans-1-bromo-2-ethoxycyclopropane (Ia)[4] to propenal diethyl acetal (IIa) (93% GLC yield) proceeds about 100 times faster than the cis isomer.[5] Fortunately, the favoured isomers (Ia, Id-If) are prepared easily by means of the carbenoid Ib obtained by bromine-lithium exchange reaction of 1,1-dibromo-2-ethoxycyclopropane (Ic)[4] with butyllithium. Reaction of Ib with electrophiles followed by thermal transformation gives 2-substituted propenal diethyl acetals II. For example, treatment of Ib at -95° with heptanal gave the corresponding adduct Id, which was

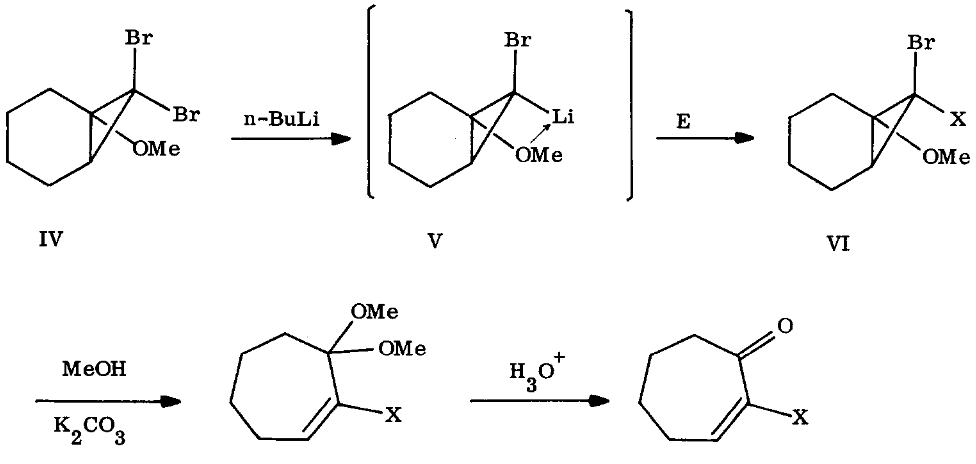


I II III

a: $X = H$; b: $X = Li$; c: $X = Br$; d: $X = CH(OH)\,n\text{-}C_6H_{13}$; e: $X = SiMe_3$; f: $X = SC_6H_5$

successively heated in ethanol in the presence of potassium carbonate to afford a diethyl acetal IId. Hydrolysis (5% H_2SO_4-THF 1:1) of IId gave an aldehyde IIId[7] isolated in 77% overall yield based on heptanal. Trimethylsilylation (80% yield) of Ib is, in particular, achieved smoothly and simply by addition of butyllithium to a mixture of Ic and trimethylsilyl chloride. Rearrangement of the resulting Ie[7] (bp 61-63°/26 Torr) gave IIe[8] (bp 88-90°/26 Torr) in 87% yield, which was in turn hydrolyzed to 2-trimethylsilylpropenal (IIIe) characterized as its 2,4-dinitrophenylhydrazone[7] (mp 153.5-154.0°, 80% yield). When diphenyldisulphide was allowed to react with the carbenoid Ib and the resulting product subjected to the subsequent transformation, 2-phenylthiopropenal (IIIf)[7] (bp 115-125° (bath temp)/0.06 Torr) was produced in 74% yield. According to the present two-step procedure, the carbenoid Ib is synthetically equivalent to 2-lithiopropenal (IIIb)[9] and provides easily 2-substituted propenal derivatives which themselves are potentially useful synthetic intermediates.[10]

The methodology described herein should be applicable also to cyclic enol ether-dibromocarbene adducts. Lithiation of 1-methoxy-7,7-dibromonorcarane (IV) with butyllithium at -95° and treatment of the resulting carbenoid V[11] with electrophile (E) afford VI whose substituents are appropriately disposed for the subsequent rearrangement.[12] Quenching V with trimethylsilyl chloride, followed by heating the resulting VIa in methanol-potassium carbonate, afforded 2-trimethylsilyl-2-cycloheptenone (VIIa, bp 147-150°/15 Torr)[7,13] under ring enlargement in 57% yield. Similarly, an enone VIIb[7,13]



IV V VI

VII

a: X = $SiMe_3$ (E = $ClSiMe_3$); b: X = CH(OH) n-C_6H_{13} (E = n-$C_6H_{13}CHO$)
c: X = $Me_2C{=}CHCH_2$ (E = $Me_2C{=}CHCH_2Br$); d: X = n-C_5H_{11} (E = n-$C_5H_{11}I$)

was obtained in 57% yield from IV and heptanal. Alkylation of the carbenoid turned out rather arduous. However, employing hexamethylphosphoric triamide as the cosolvent,[1b] we could obtain the alkylated products VIIc[7,13] and VIId[7,13] in 46% and 40% yield respectively.

Following experimental procedure is representative:

3-Hydroxy-2-methylenenonanal (IIId). At -95° a hexane solution (2.02 M) of butyllithium (5.9 ml, 12.0 mmol) was added drop by drop to 1,1-dibromo-2-ethoxycyclopropane (IIc) (2.93 g, 12.0 mmol) in tetrahydrofuran (60 ml) under an argon atmosphere. After 10 min's aging heptanal (1.14 g, 10.0 mmol) was added in one portion and the reaction mixture was stirred for 30 min at -95°, allowed to warm up to room temperature and treated with water. The organic layer was extracted with ether, dried (sodium sulphate) and concentrated *in vacuo*. The residue was heated in ethanol (15 ml) to reflux with potassium carbonate (6.90 g, 50 mmol) for 1 hr. Usual work-up gave IId,[14] which was dissolved in a mixture of tetrahydrofuran (5 ml) and 5% aq sulphuric acid (5 ml) and stirred at room temperature for 5 min. Work-up followed by purification by column chromatography gave IIId (1.32 g, 77% yield). Bp 115-120°/20 Torr. NMR (CCl_4): δ 0.7-1.6 (m, 13H), 2.20 (br s, 1H), 4.37 (t, J = 6 Hz, 1H), 5.95 (d, J = 1 Hz, 1H), 6.38 (d, J = 1 Hz, 1H), 9.52 (s, 1H); IR (neat film): 3450, 1685, 955, 908, 790 cm^{-1}; MS: m/e 170 (M^+). Found: C, 70.6; H, 10.9%. Calcd for $C_{10}H_{18}O_2$: C, 70.5; H, 10.7%.

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3. We have observed that Ic is readily converted to 2-bromopropenal diethyl acetal (IIc) in 79% yield when heated in ethanol under coexistence of potassium carbonate (5 mol).

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5. Ethanol solution of each isomer (1 M) was heated at 70° in the presence of 2 mol of potassium carbonate. The reaction was monitored by GLC assay. Pseudo first order rate constant for trans isomer was found to be 9.2×10^{-2} min^{-1}, whereas that for cis isomer 7.8×10^{-4} min^{-1}.
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7. The compound was characterized spectrometrically and analytically.
8. Characteristics of IIe are as follows: NMR (CCl_4): δ 0.03 (s, 9H), 1.10 (t, J = 6.5 Hz, 6H), 3.2-3.7 (m, 4H), 4.80 (br s, 1H), 5.45 (m, 1H), 5.80 (m, 1H); IR (neat film): 1240, 1110, 1055, 940, 840 cm^{-1}.
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11. The configuration of the carbenoid is discussed by Taylor (ref 6a) and lithium ion is found to occupy the exo position cis to methoxy group. The intramolecular coordination effect by the adjacent methoxy group seems extremely remarkable to reverse the configuration of the carbenoid predominating in the absence of the methoxy group. See ref 1b.
12. Orbital symmetry rule suggests 7-*endo*-halonorcarane is amenable to ring opening reaction under solvolytic conditions, while 7-*exo*-halo isomer remains unchanged. See R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie GmbH, Weinheim, Germany, 1970, p 56.
13. Yields are based on dibromonorcarane IV.
14. NMR (CCl_4): δ 0.6-1.6 (m + t, 19H), 2.20 (br s, 1H), 3.2-3.8 (m, 4H, $CH_3\underline{CH_2}O$), 4.05 (t, J = 5 Hz, 1H, $\underline{C}H$-OH), 4.80 (br s, 1H), 5.17 (br s, 2H, $=CH_2$); IR (neat film): 3450, 1105, 1050, 923 cm^{-1}.

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